PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15450PCT00	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/DK2004/000451	International filing date *(day/month/year)* 24.06.2004	Priority date *(day/month/year)* 25.06.2003
International Patent Classification (IPC) or national classification and IPC C07K14/47, C07K1/16		
Applicant PHARMEXA A/S et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.04.2005	14.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Schmitz, T Telephone No. +31 70 340-4494

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000451

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-37 as originally filed

   Sequence listings part of the description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-48 as originally filed

   Drawings, Sheets

   1/4-4/4 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000451

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 47, 48 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 47, 48 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000451

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-48
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-46
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000451

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/DK2004/000451

Re Item II
Priority

The claimed priority date is valid.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject matter of claims 47, 48 is directed to methods for treatment of the human or animal body by surgery or therapy and/or diagnostic methods practised on the human or animal body. For the assessment on the question as to whether this subject matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT, Rule 67.1(iv)).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication:

D1: LAROCHE-TRAINEAU J ET AL: "Three-step purification of bacterially expressed human single-chain Fv antibodies for clinical applications" JOURNAL OF CHROMATOGRAPHY. BIOMEDICAL APPLICATIONS, ELSEVIER, AMSTERDAM, NL, vol. 737, no. 1-2, January 2000 (2000-01), pages 107-117, XP004184259 ISSN: 0378-4347

D2: WO 97/24438 A (LAUS REINER ; WU HONGYU (US); RUEGG CURTIS L (US); ACTIVATED CELL THER) 10 July 1997 (1997-07-10)

2. a) Document D1, which is considered to represent the most relevant state of the

art, discloses (abstract; sections 2.3.4-2.3.6; page 116, left column, lines 1-3) a method for the purification of a recombinant protein comprising dialysis, metal affinity chromatography, size exclusion chromatography, anion exchange chromatography. From this, the subject-matter of claim 1 differs in that a method for the purification of an other protein is claimed.

The problem to be solved by present claim 1 may therefore be regarded as the provision of a method for the purification of a protein.

The solution proposed, namely the provision of a method for the purification of an EGFR family derived protein (such as HER-2) cannot be considered as involving an inventive step for the following reasons:
In view of the disclosure in document D1, the skilled person would regard it as obvious to combine several purification methods, such as those disclosed in D1 for the purification of HER-2. The skilled person would proceed without the use of inventive skill, using common knowledge and routine only, with a reasonable expectation of success.
In conclusion, the subject-matter of claim 1 does not involve an inventive step.
The subject matter of claims 2-33 does not seem to add subject matter that would render this part of the application inventive. Therefore, the subject matter of claims 1-33 does not satisfy the criterion set forth in Article 33(3) PCT.

b) The identification of a suitable purification scheme is an elaborate process which requires a lot of experimentation before a useful set of steps are found for the particular protein and raw material in question. Finding an advantageous combination of methods amongst a large number of possibilities is certainly time consuming.
However, the method as claimed is a normal combination of standard techniques, that the person skilled in the art would consider. There does at present not appear to be a surprising effect linked to the specific combination. In conclusion, no inventive step can be acknowledged at present.
If surprising effects were linked to the method for the purification of a specific protein, as might be shown by comparative examples, the objection might be reconsidered.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/DK2004/000451

3. a) Document D2, which is considered to represent the most relevant state of the art for this part of the application, discloses (abstract; SEQ ID NO:3, 4; Figure 8) a Her-2 fusion protein, having a immunostimulatory effect. From this, the subject-matter of claim 34 differs in that a different HER-2 variant is claimed. SEQ ID NO:4 has 94.8% identity in a 660 amino acid overlap (33-692:20-674) with present SEQ ID NO:2.

The problem to be solved by present claim 34 may therefore be regarded as the provision of a HER-2 variant.

The solution proposed, namely the provision of a further HER-2 variant as defined by SEQ ID NO:2 cannot be considered as involving an inventive step for the following reasons:
In view of the disclosure in document D2, the skilled person would regard it as obvious to provide further variants of said protein. The skilled person would proceed without the use of inventive skill, using common knowledge only, with a reasonable expectation of success.

In conclusion, **in the absence of a surprising effect**, the subject-matter of claim 34 does not involve an inventive step. The subject matter of claims 35-48 does not seem to add subject matter that would render this part of the invention inventive. Therefore, the subject matter of claims 33-48 does not satisfy the criterion set forth in Article 33(3) PCT.

b) An inventive step for the claimed protein might be acknowledged if the protein imparted unexpected properties, such as the combination of superior stability, immunogenicity, 3D structure and induction of high quality antibody, when compared to other Her-2 fusions. However, no evidence for such unexpected properties was submitted.